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REVIEW

# OATPs, OATs and OCTs: the organic anion and cation transporters of the *SLCO* and *SLC22A* gene superfamilies

Megan Roth[1], Amanda Obaidat[1] and Bruno Hagenbuch[1,2]

[1]*Department of Pharmacology, Toxicology and Therapeutics, The University of Kansas Medical Center, Kansas City, KS, USA, and* [2]*The University of Kansas Cancer Center, Kansas City, KS, USA*

**Correspondence**
Bruno Hagenbuch, Department of Pharmacology, Toxicology and Therapeutics, The University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160, USA. E-mail: bhagenbuch@kumc.edu

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The human organic anion and cation transporters are classified within two *SLC* superfamilies. Superfamily *SLCO* (formerly *SLC21A*) consists of organic anion transporting polypeptides (OATPs), while the organic anion transporters (OATs) and the organic cation transporters (OCTs) are classified in the *SLC22A* superfamily. Individual members of each superfamily are expressed in essentially every epithelium throughout the body, where they play a significant role in drug absorption, distribution and elimination. Substrates of OATPs are mainly large hydrophobic organic anions, while OATs transport smaller and more hydrophilic organic anions and OCTs transport organic cations. In addition to endogenous substrates, such as steroids, hormones and neurotransmitters, numerous drugs and other xenobiotics are transported by these proteins, including statins, antivirals, antibiotics and anticancer drugs. Expression of OATPs, OATs and OCTs can be regulated at the protein or transcriptional level and appears to vary within each family by both protein and tissue type. All three superfamilies consist of 12 transmembrane domain proteins that have intracellular termini. Although no crystal structures have yet been determined, combinations of homology modelling and mutation experiments have been used to explore the mechanism of substrate recognition and transport. Several polymorphisms identified in members of these superfamilies have been shown to affect pharmacokinetics of their drug substrates, confirming the importance of these drug transporters for efficient pharmacological therapy. This review, unlike other reviews that focus on a single transporter family, briefly summarizes the current knowledge of all the functionally characterized human organic anion and cation drug uptake transporters of the *SLCO* and the *SLC22A* superfamilies.

## LINKED ARTICLES

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## Abbreviations

ABC, ATP-binding cassette; BSP, bromosulphophthalein; CCK-8, cholecystokinin-octapeptide; CoMFA, comparative molecular field analysis; HNF, hepatocyte nuclear factor; MPP, 1-methyl-4-phenylpyridinium; NSAID, non-steroidal anti-inflammatory drug; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation and carnitine transporter; PAH, p-aminohippurate; SHP, small heterodimer partner; SLC, solute carrier; SNP, single nucleotide polymorphism; SXR, steroid and xenobiotic receptor; TEA, tetraethylammonium; URAT, urate transporter

## General introduction

Numerous endo- and xenobiotics including many drugs are organic anions or cations. Their disposition and elimination depend on the proper function of multispecific drug transporters that belong to two major superfamilies: solute carrier (SLC) transporters and ATP-binding cassette (ABC) transporters. Although most are capable of bidirectional transport, in

general, ABC transporters are considered to be responsible for efflux of substrates, while SLC transporters mediate uptake of substrates into cells. Within the SLC transporters, there are two gene superfamilies that contain the major organic anion and cation transporters. These are the *SLCO* superfamily, made up of the organic anion transporting polypeptides (OATPs), and the *SLC22A* superfamily, which contains the organic cation transporters (OCTs) and the organic anion transporters (OATs). Individual members of these superfamilies are expressed in essentially every epithelium throughout the body. The members of both superfamilies mediate transport of a broad range of structurally diverse compounds with overlapping substrate specificities within the superfamilies. In general, OCTs transport cations, OATPs transport large and fairly hydrophobic organic anions, and OATs transport the smaller and more hydrophilic organic anions. This brief review will summarize our current knowledge about the human members of these three transporter families, with an emphasis on tissue distribution, substrate specificity, regulation of expression, transporter structure and pathology.

## Nomenclature

OATPs are encoded by genes in the *SLCO/Slco* superfamily. This superfamily was originally named *SLC21A*; however, the nomenclature of its members was updated and standardized in 2004 based on phylogenetic relationships, and the superfamily was renamed to *SLCO*, the solute carrier family of the OATPs (Hagenbuch and Meier, 2004). Eleven human OATPs have been identified and are classified into six families based on their amino acid identity. The different proteins are named OATP (Oatp for the rodent proteins) followed by the family number (e.g. OATP1, OATP2), the subfamily letter (e.g. OATP1A, OATP1B) and then a consecutive number identifying the individual members within the family based on the historical order in which they have been identified (e.g. Oatp1a1, OATP1A2 and Oatp1a3). The corresponding gene symbols are *SLCO* followed by the same number–letter–number combination (e.g. *Slco1a1*, *SLCO1A2* and *Slco1a3*). The best characterized OATPs belong to family 1, which in humans contains OATP1A2, OATP1B1, OATP1B3 and OATP1C1. A significant amount of gene duplication and divergence has occurred in this family, especially in rodents, complicating direct comparisons between human (OATP) and rodent (Oatp) studies. OATP1A2 has five rodent orthologues: Oatp1a1, Oatp1a3 (in rats only), Oatp1a4, Oatp1a5 and Oatp1a6. OATP1B1 and OATP1B3 have a single rodent orthologue, Oatp1b2. The other OATPs and their rodent orthologues are OATP1C1 (Oatp1c1), OATP2A1 (Oatp2a1), OATP2B1 (Oatp2b1), OATP3A1 (Oatp3a1), OATP4A1 (Oatp4a1), OATP4C1 (Oatp4c1), OATP5A1 and OATP6A1 (Oatp6b1, Oatp6c1 and Oatp6d1).

The *SLC22A* family includes OCT1-3 (*SLC22A1-3*), OCTN1 and OCTN2 (*SLC22A4-5*), OCT6 (*SLC22A16*, also known as CT2), OAT1-4 (*SLC22A6-8, 11*), OAT7 (*SLC22A9*), URAT1 (*SLC22A12*) and several additional not well characterized putative transporters. Most of these proteins have a single rodent orthologue, but OAT4 is specific to humans. OAT5 (*SLC22A10*) was cloned in 2001 but has not been functionally characterized (Sun *et al.*, 2001); thus, it is considered an orphan OAT. It is believed that human OAT5 is not the orthologue of rodent Oat5 (Youngblood and Sweet, 2004). Additionally, in rodents, there is an Octn3 protein (*Slc22a21*) – although no human homologue has been conclusively identified, an antibody against mouse Octn3 cross-reacts in certain human tissues, which led the authors to suggest that a human OCTN3 does exist (Lamhonwah *et al.*, 2005). The human and rodent *SLCO* and *SLC* genes and their corresponding proteins are listed in Table 1. Unless otherwise stated, all information included in this review refers to the human transporters.

## OATPs

Organic anion transporting polypeptides (OATPs in humans, Oatps in rodents) are multispecific transporters located in numerous epithelia throughout the body. They mediate the cellular uptake of a broad range of substrates, including bile acids, steroid conjugates and numerous xenobiotics.

### *Tissue distribution*

Protein expression for OATPs is summarized in Figure 1. OATP1A2 is widely distributed throughout the body, with the highest mRNA expression in the brain, liver, lung, kidney and testes (Kullak-Ublick *et al.*, 1995; Steckelbroeck *et al.*, 2004). With this distribution, it is thought that OATP1A2 could play a critical role in the absorption, distribution and excretion of xenobiotics. OATP1A2 protein has been localized to the brush border membrane of enterocytes in the duodenum (Glaeser *et al.*, 2007), where it may mediate the absorption of xenobiotics. Within the liver, OATP1A2 is exclusively expressed in cholangiocytes (Lee *et al.*, 2005) and may be involved in the reabsorption of xenobiotics excreted into the bile. In the kidney, OATP1A2 is expressed at the apical membrane of the distal nephron (Lee *et al.*, 2005), where it could be responsible for either the reabsorption from or the secretion of xenobiotics into urine. OATP1A2 is also expressed at the luminal membrane of the endothelial cells of brain capillaries (Bronger *et al.*, 2005) and is thought to be part of the blood–brain barrier. OATP1B1 and OATP1B3 are both selectively expressed in the liver (Abe *et al.*, 1999; 2001; Hsiang *et al.*, 1999; Konig *et al.*, 2000a,b), where they are localized to the basolateral membrane of hepatocytes (Konig *et al.*, 2000b; Abe *et al.*, 2001; Kullak-Ublick *et al.*, 2001; Cui *et al.*, 2003). OATP1B1 is expressed in hepatocytes throughout the lobule, while OATP1B3 is primarily expressed around the central vein (Konig *et al.*, 2000a); consistent with this pattern, expression levels of OATP1B1 mRNA in liver homogenate are higher overall than are levels of OATP1B3 (Michalski *et al.*, 2002; Briz *et al.*, 2006). OATP1C1 mRNA expression was originally localized to the brain and testes (Pizzagalli *et al.*, 2002), and OATP1C1 protein has been detected at the basolateral membrane of choroid plexus epithelial cells (Roberts *et al.*, 2008) and to the Leydig cells of the testes (Pizzagalli *et al.*, 2002).

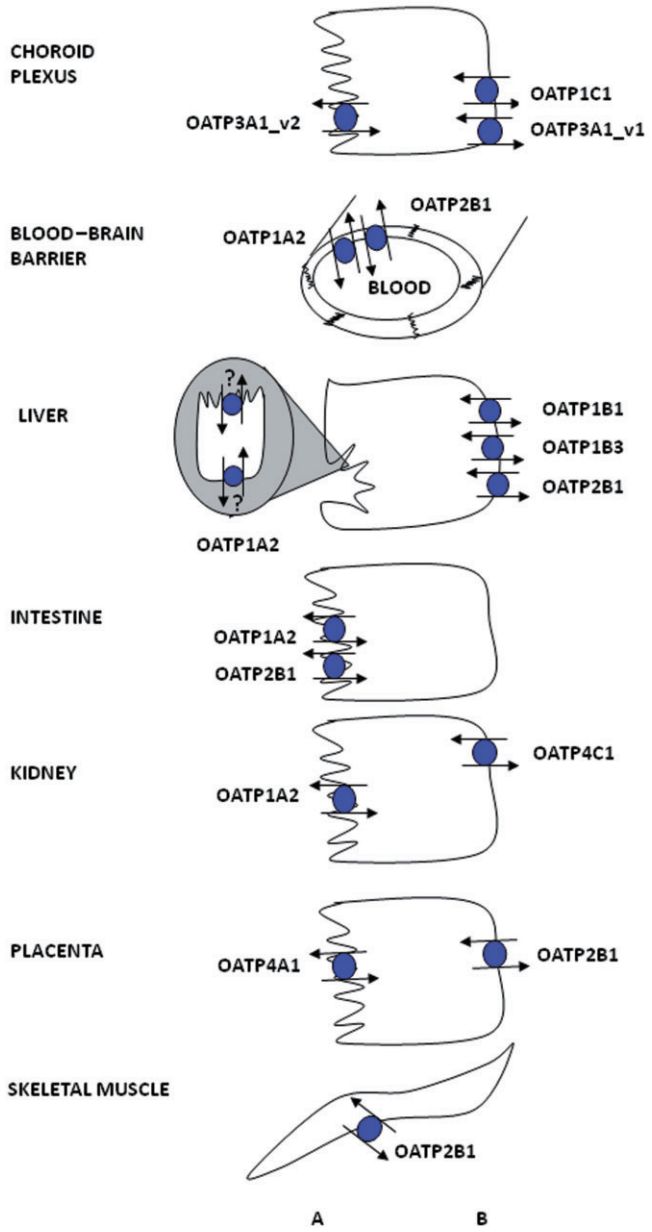
OATP2A1, also known as the prostaglandin transporter (PGT), is ubiquitously expressed throughout the body (Nomura *et al.*, 2004; 2005). As shown by Northern blot analysis, mRNA of OATP2A1 was found in several tissues including brain, colon, heart, kidney, liver, lung, ovary, pan-

## Table 1

Gene and protein names of human and rodent organic anion and cation transporters

| Human gene | Human protein | Rodent gene | Rodent protein |
|---|---|---|---|
| | | *Slco1a1* | Oatp1a1 |
| *SLCO1A2* | OATP1A2 | | |
| | | *Slco1a3* (rat only) | Oatp1a3 |
| | | *Slco1a4* | Oatp1a4 |
| | | *Slco1a5* | Oatp1a5 |
| | | *Slco1a6* | Oatp1a6 |
| *SLCO1B1* | OATP1B1 | | |
| | | *Slco1b2* | Oatp1b2 |
| *SLCO1B3* | OATP1B3 | | |
| *SLCO1C1* | OATP1C1 | *Slco1c1* | Oatp1c1 |
| *SLCO2A1* | OATP2A1 | *Slco2a1* | Oatp2a1 |
| *SLCO2B1* | OATP2B1 | *Slco2b1* | Oatp2b1 |
| *SLCO3A1* | OATP3A1 | *Slco3a1* | Oatp3a1 |
| *SLCO4A1* | OATP4A1 | *Slco4a1* | Oatp4a1 |
| *SLCO4C1* | OATP4C1 | *Slco4c1* | Oatp4c1 |
| *SLCO5A1* | OATP5A1 | | |
| *SLCO6A1* | OATP6A1 | | |
| | | *Slco6b1* | Oatp6b1 |
| | | *Slco6c1* | Oatp6c1 |
| | | *Slco6d1* | Oatp6d1 |
| *SLC22A1* | OCT1 | *Slc22a1* | Oct1 |
| *SLC22A2* | OCT2 | *Slc22a2* | Oct2 |
| *SLC22A3* | OCT3 | *Slc22a3* | Oct3 |
| *SLC22A4* | OCTN1 | *Slc22a4* | Octn1 |
| *SLC22A5* | OCTN2 | *Slc22a5* | Octn2 |
| *SLC22A6* | OAT1 | *Slc22a6* | Oat1 |
| *SLC22A7* | OAT2 | *Slc22a7* | Oat2 |
| *SLC22A8* | OAT3 | *Slc22a8* | Oat3 |
| *SLC22A9* | OAT7 | | |
| *SLC22A10* | OAT5 | | |
| *SLC22A11* | OAT4 | | |
| *SLC22A12* | URAT1 | *Slc22a12* | Urat1 |
| *SLC22A13* | OAT10 | *Slc22a13* | Oat10 |
| *SLC22A16* | OCT6 (CT2) | | |
| | | *Slc22a19* | Oat5 |
| *SLC22A20* | OAT6 | *Slc22a20* | Oat6 |
| | | *Slc22a21* | Octn3 |

creas, placenta, prostate, skeletal muscle, spleen and small intestine (Schuster, 2002). Recently, OATP2A1 protein expression was shown in the upper gastrointestinal tract, localized in the pyloric glands of the antrum and parietal cells of the gastric corpus (Mandery *et al.*, 2010). OATP2A1 is thought to be involved in terminating prostaglandin signalling by transporting prostaglandins into cells (Nomura *et al.*, 2004; 2005). OATP2B1 is also widely expressed throughout the body (Tamai *et al.*, 2000; Kullak-Ublick *et al.*, 2001). The highest levels of mRNA are found in the liver, where the protein is located at the basolateral membrane of hepatocytes (Kullak-Ublick *et al.*, 2001). Protein expression has also been reported at the apical membrane of intestinal epithelial cells (Kobayashi *et al.*, 2003), at the basolateral membrane of syncytiotrophoblasts in the placenta (St-Pierre *et al.*, 2002), in epidermal keratinocytes (Schiffer *et al.*, 2003), in the myoepi-




## Figure 1

Expression of OATPs in selected human epithelial cells. For more details, see the text. OATP1A2 expression in cholangiocytes has been demonstrated, but it has not yet been localized to a distinct cell membrane. (A) apical; (B) basolateral.

thelium surrounding ductal epithelial cells in human mammary gland (Pizzagalli *et al.*, 2003), in vascular endothelial cells in the heart (Grube *et al.*, 2006b), in skeletal muscle (Knauer *et al.*, 2010) and at the luminal membrane of the endothelial cells of the blood–brain barrier (Bronger *et al.*, 2005).

OATP3A1 mRNA levels are highest in testes, brain and heart followed by lung, spleen, peripheral blood leukocytes and thyroid gland (Adachi *et al.*, 2003; Huber *et al.*, 2007). OATP3A1 mRNA expression has also been shown in human epidermal keratinocytes (Schiffer *et al.*, 2003). OATP3A1 has two splice variants, which have cell type-specific expression. OATP3A1_v1 was localized to the germ cells of testes, at the basolateral membrane of the choroid plexus and in neuroglial cells of the grey matter in the frontal cortex, while OATP3A1_v2 was localized in the Sertoli cells of the testes, at the apical and sub-apical membrane in choroid plexus and in cell bodies and axons of the neurons in the frontal cortex (Huber *et al.*, 2007).

OATP4A1 has been detected in several tissues with the highest levels of mRNA found in the heart and placenta, followed by lung, liver, skeletal muscle, kidney and pancreas (Tamai *et al.*, 2000; Fujiwara *et al.*, 2001). OATP4A1 protein was localized to the apical membrane of syncytiotrophoblasts in the placenta (Sato *et al.*, 2003). OATP4C1 was initially thought to be a kidney-specific OATP, based on Northern blot analysis (Mikkaichi *et al.*, 2004). Based on the localization of rat Oatp4c1, it is assumed that human OATP4C1 is also localized at the basolateral membrane of proximal tubule cells. A recent microarray suggests that OATP4C1 may also be expressed in the liver, although this has not yet been verified by RT-PCR or protein analysis (Bleasby *et al.*, 2006). This microarray also contains the only determination of OATP5A1 expression to date, showing possible expression in fetal brain, prostate, skeletal muscle and thymus. OATP6A1 mRNA has been shown mainly in the testes, with low expression in spleen, brain, fetal brain and placenta (Suzuki *et al.*, 2003; Lee *et al.*, 2004).

## *Substrate specificity*

The mechanism of OATP-mediated transport remains controversial. It is well established that transport is ATP- and sodium-independent, but the driving force for transport is still under investigation. OATPs are capable of bidirectional transport, and several studies have suggested that they work as electroneutral exchangers. Evidence suggests that individual OATPs/Oatps may exchange their substrates for intracellular bicarbonate (Satlin *et al.*, 1997; Leuthold *et al.*, 2009), glutathione (Li *et al.*, 1998; Franco and Cidlowski, 2006) or glutathione conjugates (Li *et al.*, 2000). However, it appears that there could be differences among the different OATPs/Oatps with respect to the exact transport mechanism: for example, transport mediated by OATP1B1 and OATP1B3 is not affected by glutathione (Mahagita *et al.*, 2007).

OATP-mediated transport can also be affected by pH. Several studies have shown that OATP2B1 transport activity is increased at acidic pH (Kobayashi *et al.*, 2003; Nozawa *et al.*, 2004a; Sai *et al.*, 2006; Varma *et al.*, 2011). As OATP2B1 is expressed in the small intestine, this phenomenon could result in both increased transport of substrates and a broader substrate range and thus improve OATP2B1-mediated drug absorption. However, this effect seems to be substrate dependent and can be caused by both increased affinity (decreased $K_m$) and increased turnover rate ($V_{max}$) (Nozawa *et al.*, 2004a; Leuthold *et al.*, 2009). It has been proposed that the mechanism of increased substrate affinity is caused by the protonation of a conserved histidine residue at the extracellular end of transmembrane domain 3 (Leuthold *et al.*, 2009). Transport of estrone-3-sulphate by OATP1B1 and OATP1B3 has previously been shown to be independent of the extracellular pH and of the membrane potential (Mahagita *et al.*, 2007). However, a recent report demonstrates that these two trans-

porters are influenced in different ways by both pH and the membrane potential (Martinez-Becerra *et al.*, 2011).

To determine the driving force of OATP-mediated transport, additional studies are clearly needed. By using membrane vesicles isolated from cells that overexpress individual OATPs, the exact composition of the buffers on both sides of the plasma membrane can be controlled. Based on such experiments, an exact delineation of the involved driving forces and exchange mechanisms should be possible.

Most OATPs transport a broad range of compounds. The transported substrates are summarized for family OATP1 in Table 2, for family OATP2 in Table 3 and for all the remaining OATPs in Table 4 (no substrates have yet been identified for OATP5A1 or OATP6A1). Although the majority of substrates are anions, some OATPs can also transport neutral and cationic compounds (Bossuyt *et al.*, 1996). In general, substrates are amphipathic molecules with molecular weights greater than 350 Daltons and include bile acids, conjugated steroids, thyroid hormones, linear and cyclic peptides and mushroom toxins as well as numerous drugs, including statins, sartans, antibiotics and anticancer drugs. Many of these compounds (e.g. estrone-3-sulphate, estradiol-17β-glucuronide or bromosulphophthalein) are substrates of multiple OATPs and are therefore commonly used as model substrates. However, some substrates appear to be more specific; for example, cholecystokinin-octapeptide (CCK-8) is selectively transported by OATP1B3 (Ismair *et al.*, 2001), while digoxin seems to be mainly transported by OATP4C1 (Mikkaichi *et al.*, 2004).

It has been suggested that substrates are transported through a central positively charged pore in OATPs via a rocker-switch mechanism (Meier-Abt *et al.*, 2005). A pharmacophore model developed for OATP1B1 based on published apparent $K_m$ values of OATP substrates suggests that substrates contain two hydrogen bond acceptors, one hydrogen bond donor and two hydrophobic regions (Chang *et al.*, 2005). A CoMFA (comparative molecular field analysis) model calculated based on 25 competitive inhibitors suggested that the substrate binding site for estradiol-17β-glucuronide on OATP1B1 consists of a large hydrophobic region with basic residues at both ends (Gui *et al.*, 2009). However, such analyses are complicated by the indication that OATPs have multiple substrate binding sites or translocation pathways. OATP1B1 has biphasic saturation kinetics for estrone-3-sulphate, suggesting the presence of both a high-affinity, low-capacity binding site and a low-affinity, high-capacity binding site (Tamai *et al.*, 2001; Noe *et al.*, 2007; Gui and Hagenbuch, 2009). Similarly, OATP4C1 was recently shown to have distinct binding sites for estrone-3-sulphate and digoxin (Yamaguchi *et al.*, 2010). In addition, inhibition studies have shown that compounds can have stimulatory, inhibitory or no effect on OATP-mediated transport, depending on the model substrate used (Gui *et al.*, 2008; Roth *et al.*, 2011a,b).

## Regulation of expression

Expression of OATPs is largely controlled by transcriptional regulation. Constitutive OATP1B1 expression in hepatocytes appears to be dependent on HNF1α (Jung and Kullak-Ublick, 2003; Furihata *et al.*, 2007), while OATP1B3 is likely regulated by HNF3β (Vavricka *et al.*, 2004). There is also evidence that additional signals may be involved in OATP1B expression, including Stat5 (Wood *et al.*, 2005) and transcription factors activated by hepatocyte growth factor (Le Vee *et al.*, 2009), IFN-γ (Le Vee *et al.*, 2011) and IL-1β (Le Vee *et al.*, 2008). The mechanisms for regulating OATP expression are likely to vary by tissue type. For example, OATP1A2 expression is up-regulated in response to increased bile acid levels (Kullak-Ublick *et al.*, 1997a), which would affect expression levels in the small intestine and liver. In breast carcinoma tissues and cell lines, however, OATP1A2 expression is significantly associated with the steroid and xenobiotic receptor (SXR) expression (Miki *et al.*, 2006).

Regulation of OATPs can also occur at the protein level. As most OATPs contain a PDZ consensus sequence (Wang *et al.*, 2005a), and the carboxy-terminus of OATP1A2 has been shown to interact with PDZ proteins (Kato *et al.*, 2004), membrane localization of OATPs may be due to interactions with PDZ proteins. A recent study with rat Oatp1a1 demonstrated that in addition to the interaction with PDZ proteins, phosphorylation affected membrane expression (Choi *et al.*, 2011). It has also been shown that activation of PKC leads to the phosphorylation of OATP2B1 and a reduced $V_{max}$ for substrates, suggesting that the protein is internalized upon phosphorylation (Kock *et al.*, 2010).

## Transporter structure

Human OATPs range in size from 643 to 724 amino acids, with the exception of the as yet uncharacterized OATP5A1, which contains 848 amino acids. OATPs are predicted to contain 12 transmembrane domains, with both termini located intracellularly. Although hydropathy models predict either a 10- or 12-domain topology, the 12-transmembrane domain model was confirmed for rat Oatp1a1 (Wang *et al.*, 2008). The second and fifth extracellular loops contain multiple predicted and/or confirmed N-glycosylation sites, although the exact location varies by protein. The large fifth extracellular loop contains many conserved cysteines, which have been shown to be involved in disulphide bonds and are important for the surface expression of OATP2B1 (Hanggi *et al.*, 2006). Similar to most other mammalian transport proteins, there is no crystal structure available for any of the OATPs so far. Therefore, homology modelling has been used to construct putative three-dimensional models of OATPs; this aids in the generation of theoretical predictions that can then be tested experimentally (Meier-Abt *et al.*, 2005; Gui and Hagenbuch, 2008; Glaeser *et al.*, 2010). Based on such models, several conserved positively charged amino acids that line the putative substrate pore were studied, and amino acids R57, K361 and R580 in OATP1B1 (Weaver and Hagenbuch, 2010) and K41, R580 and K361 in OATP1B3 (Glaeser *et al.*, 2010; Mandery *et al.*, 2011) were shown to be important for substrate transport. These amino acids are highlighted in the predicted three-dimensional structure of OATP1B1 shown in Figure 2A. Additional experiments using chimeras between OATP1B1 and OATP1B3 identified transmembrane domains 8 and 9 for OATP1B1 (Miyagawa *et al.*, 2009) and transmembrane domain 10 for both OATP1B1 (Gui and Hagenbuch, 2009) and OATP1B3 (Gui and Hagenbuch, 2008) to be important for substrate transport and expression.

## Table 2

Substrates of human OATP1 family

| Substrates | $K_m$ (μM) | References |
|---|---|---|
| OATP1A2 | | |
| Acebutolol | | Kato *et al.* (2009) |
| APD-ajmalinium | | Bossuyt *et al.* (1996); van Montfoort *et al.* (1999) |
| Atenolol | | Kato *et al.* (2009) |
| Atrasentan | | Katz *et al.* (2006) |
| Bamet-R2 | 24 | Briz *et al.* (2002) |
| Bamet-UD2 | 14 | Briz *et al.* (2002) |
| Bilirubin | | Briz *et al.* (2003) |
| BQ-123 | | Kullak-Ublick *et al.* (2001) |
| Bromosulphophthalein | 20 | Kullak-Ublick *et al.* (1995) |
| Celiprolol | 20.5 | Kato *et al.* (2009) |
| Chlorambucil-taurocholate | | Kullak-Ublick *et al.* (1997b) |
| Cholate | 93 | Kullak-Ublick *et al.* (1995); Meier *et al.* (1997) |
| Ciprofloxacin | | Maeda *et al.* (2007) |
| CRC220 | | Meier *et al.* (1997) |
| Darunavir | | Hartkoorn *et al.* (2010) |
| Dehydroepiandrosterone-3-sulphate | 7 | Kullak-Ublick *et al.* (1998) |
| Deltorphin II | 330 | Gao *et al.* (2000) |
| [D-penicillamine$^{2,5}$]enkephalin | 202 | Gao *et al.* (2000) |
| Enoxacin | | Maeda *et al.* (2007) |
| Epicatechin gallate | 10 | Roth *et al.* (2011b) |
| Epigallocatechin gallate | 19 | Roth *et al.* (2011b) |
| Erythromycin | | Franke *et al.* (2008) |
| Estradiol-17β-glucuronide | | Meier *et al.* (1997); Kullak-Ublick *et al.* (2001); Briz *et al.* (2003) |
| Estrone-3-sulphate | 16 | Lee *et al.* (2005) |
| Fexofenadine | 6 | Cvetkovic *et al.* (1999) |
| Gatifloxacin | | Maeda *et al.* (2007) |
| Gd-B20790 | | Pascolo *et al.* (1999) |
| Glycocholate | | Kullak-Ublick *et al.* (1995; 2001); Meier *et al.* (1997) |
| Hydroxyurea | | Walker *et al.* (2011) |
| Imatinib | | Hu *et al.* (2008) |
| Labetalol | | Kato *et al.* (2009) |
| Levofloxacin | 136 | Maeda *et al.* (2007) |
| Lomefloxacin | | Maeda *et al.* (2007) |
| Lopinavir | | Hartkoorn *et al.* (2010) |
| Methotrexate | 457 | Badagnani *et al.* (2006) |
| Microcystin | 20 | Fischer *et al.* (2005) |
| N-methylquinidine | 26 | van Montfoort *et al.* (1999) |
| N-methylquinine | 5 | van Montfoort *et al.* (1999); Kullak-Ublick *et al.* (2001) |
| Nadolol | | Kato *et al.* (2009) |
| Norfloxacin | | Maeda *et al.* (2007) |
| Ouabain | 5 500 | Bossuyt *et al.* (1996) |
| Pitavastatin | 3 | Fujino *et al.* (2005) |
| $PGE_2$ | | Kullak-Ublick *et al.* (2001) |
| Reverse triiodothyronine (rT3) | | Fujiwara *et al.* (2001) |
| Rocuronium | | van Montfoort *et al.* (1999) |

## Table 2

*Continued*

| Substrates | $K_m$ (μM) | References |
|---|---|---|
| Rosuvastatin | 3 | Ho *et al.* (2006) |
| Saquinavir | 36 | Su *et al.* (2004) |
| Sotalol | | Kato *et al.* (2009) |
| Talinolol | 714 | Shirasaka *et al.* (2010) |
| Taurocholate | 60 | Kullak-Ublick *et al.* (1995) |
| Taurochenodeoxycholate | | Kullak-Ublick *et al.* (1995) |
| Tauroursodeoxycholate | 19 | Kullak-Ublick *et al.* (1995) |
| Thyroxine (T4) | 8 | Fujiwara *et al.* (2001) |
| Tebipenem pivoxil | 41 | Kato *et al.* (2010) |
| TR-14035 | | Tsuda-Tsukimoto *et al.* (2006) |
| Triiodothyronine (T3) | 7 | Fujiwara *et al.* (2001) |
| Unoprostone metabolite | 93 | Gao *et al.* (2005) |
| OATP1B1 | | |
| ACU154 | | Takada *et al.* (2004) |
| Arsenic (arsenite, arsenate) | | Lu *et al.* (2006) |
| Atorvastatin | 10 | Lau *et al.* (2007) |
| Atrasentan | | Katz *et al.* (2006) |
| Bamet-R2 | 10 | Briz *et al.* (2002) |
| Bamet-UD2 | 10 | Briz *et al.* (2002) |
| Benzylpenicillin | | Tamai *et al.* (2000) |
| BDE47 | 0.31 | Pacyniak *et al.* (2010) |
| BDE99 | 0.91 | Pacyniak *et al.* (2010) |
| BDE153 | 1.91 | Pacyniak *et al.* (2010) |
| Bilirubin | 0.01 | Briz *et al.* (2003) |
| Bisglucuronosyl bilirubin | 0.3 | Cui *et al.* (2001) |
| BNP1350 | | Oostendorp *et al.* (2009) |
| Bosentan | 44 | Treiber *et al.* (2007) |
| BQ-123 | | Kullak-Ublick *et al.* (2001) |
| Bromosulphophthalein | 0.1–0.3 | Cui *et al.* (2001); Kullak-Ublick *et al.* (2001) |
| Caspofungin | | Sandhu *et al.* (2005) |
| Cefazolin | 20 800 | Nakakariya *et al.* (2008) |
| Cefditoren | 3 450 | Nakakariya *et al.* (2008) |
| Cefoperazone | 4 840 | Nakakariya *et al.* (2008) |
| Cerivastatin | 4 | Shitara *et al.* (2003) |
| CDCA-NBD | 1.5 | Yamaguchi *et al.* (2006) |
| Cholate | 11 | Cui *et al.* (2001) |
| Cholyl-glycylamido-fluorescein (CGamF) | 7.9 | Annaert *et al.* (2010) |
| [D-Ala2, D-Leu5]enkephalin | | Nozawa *et al.* (2003) |
| Darunavir | | Hartkoorn *et al.* (2010) |
| Dehydroepiandrosterone-3-sulphate | 22 | Abe *et al.* (1999; 2001); Hsiang *et al.* (1999); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001) |
| Demethylphalloin | 17 | Meier-Abt *et al.* (2004) |
| [D-penicillamine$^{2,5}$]enkephalin | | Abe *et al.* (2001) |
| Eltrombopag | | Takeuchi *et al.* (2011) |
| Enalapril | 262 | Liu *et al.* (2006) |

## Table 2

*Continued*

| Substrates | $K_m$ (μM) | References |
|---|---|---|
| Estradiol-17β-glucuronide | 4–24 | Abe *et al.* (1999); Tamai *et al.* (2000; 2001); Konig *et al.* (2000b); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001); Nakai *et al.* (2001); Hirano *et al.* (2004) |
| Estrone-3-sulphate | 0.5<br>12.5 | Hirano *et al.* (2004)<br>Cui *et al.* (2001) |
| | 0.09 and 5.4 | Tamai *et al.* (2001) |
| | 0.23 and 45 | Noe *et al.* (2007) |
| Ezetimibe glucuronide | | Oswald *et al.* (2008) |
| Fluorescein | | Gui *et al.* (2010) |
| Fluorescein methotrexate | 3.8 | Gui *et al.* (2010) |
| Fluvastatin | 1.4–3.5 | Kopplow *et al.* (2005); Noe *et al.* (2007) |
| Gimatecan | | Oostendorp *et al.* (2009) |
| Glycocholate | | Kullak-Ublick *et al.* (2001) |
| Glycoursodeoxycholate | | Maeda *et al.* (2006b) |
| Hydroxyurea | | Walker *et al.* (2011) |
| Leukotriene C4 | | Abe *et al.* (1999) |
| Leukotriene E4 | | Abe *et al.* (1999) |
| Lopinavir | | Hartkoorn *et al.* (2010) |
| Mesalazine | 55 | Konig (2011) |
| Methotrexate | | Abe *et al.* (2001) |
| Microcystein | 7 | Fischer *et al.* (2005) |
| Monoglyucuronosyl bilirubin | 0.1 | Cui *et al.* (2001) |
| Mycophenolic acid-7-O-glucuronide | | Picard *et al.* (2010) |
| Nafcillin | 1 110 | Nakakariya *et al.* (2008) |
| Olmesartan | 13–43 | Nakagomi-Hagihara *et al.* (2006); Yamada *et al.* (2007) |
| Phalloidin | 17–39 | Fehrenbach *et al.* (2003); Meier-Abt *et al.* (2004) |
| Pitavastatin | 3–4 | Hirano *et al.* (2004); Fujino *et al.* (2005) |
| Pravastatin | 14–34 | Hsiang *et al.* (1999); Nakai *et al.* (2001); Sasaki *et al.* (2002) |
| PG $E_2$ | | Abe *et al.* (1999); Tamai *et al.* (2000); Kullak-Ublick *et al.* (2001) |
| Rifampicin | 2–13 | Vavricka *et al.* (2002); Tirona *et al.* (2003) |
| Ro 48-5033 | 60 | Treiber *et al.* (2007) |
| Rosuvastatin | 9 | Ho *et al.* (2006) |
| S-8921G | 1.93 | Sakamoto *et al.* (2008) |
| Saquinavir | | Hartkoorn *et al.* (2010) |
| Simvastatin acid | | Pasanen *et al.* (2006) |
| SN-38 | | Nozawa *et al.* (2005) |
| Taurocholate | 10–34 | Abe *et al.* (1999; 2001); Hsiang *et al.* (1999); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001) |
| Tauroursodeoxycholate | 7.5 | Maeda *et al.* (2006b) |
| Temocapril | | Maeda *et al.* (2006a) |
| Thromboxane B2 | | Abe *et al.* (1999) |
| Thyroxine (T4) | 3 | Abe *et al.* (1999) |
| Torasemide | 6.2 | Vormfelde *et al.* (2008); Werner *et al.* (2008) |
| TR-14035 | 7.5 | Tsuda-Tsukimoto *et al.* (2006) |
| Triiodothyronine (T3) | 3 | Abe *et al.* (1999) |
| Troglitazone sulphate | | Nozawa *et al.* (2004b) |
| Valsartan | 1.4 | Yamashiro *et al.* (2006) |

## Table 2

*Continued*

| Substrates | $K_m$ (μM) | References |
|---|---|---|
| OATP1B3 | | |
| Amanitin | 4 | Letschert *et al.* (2006) |
| Atrasentan | | Katz *et al.* (2006) |
| Benzylpenicillin (Penicillin G) | | Letschert *et al.* (2006) |
| BDE47 | 0.41 | Pacyniak *et al.* (2010) |
| BDE99 | 0.70 | Pacyniak *et al.* (2010) |
| BDE153 | 1.66 | Pacyniak *et al.* (2010) |
| Bilirubin | 0.04 | Briz *et al.* (2003) |
| Bosentan | 141 | Treiber *et al.* (2007) |
| BQ-123 | | Kullak-Ublick *et al.* (2001) |
| Bromosulphophthalein | 0.4–6 | Kullak-Ublick *et al.* (2001) |
| Cefadroxil | 4150 | Nakakariya *et al.* (2008) |
| Cefazolin | 3890 | Nakakariya *et al.* (2008) |
| Cefditoren | 5870 | Nakakariya *et al.* (2008) |
| Cefmetazole | 706 | Nakakariya *et al.* (2008) |
| Cefoperazone | 1950 | Nakakariya *et al.* (2008) |
| Cephalexin | 1190 | Nakakariya *et al.* (2008) |
| CDCA-NBD | 0.5 | Yamaguchi *et al.* (2006) |
| Cholate | 42 | Briz *et al.* (2006) |
| Cholecystokinin octapeptide (CCK-8) | 4–11 | Ismair *et al.* (2001); Hirano *et al.* (2004) |
| Cholyl-glycylamido-fluorescein (CGamF) | 2.2 | Annaert *et al.* (2010) |
| Dehydroepiandrosterone-3-sulphate | | Konig *et al.* (2000a); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001) |
| Deltorphin II | | Kullak-Ublick *et al.* (2001) |
| Demethylphalloin | 8 | Meier-Abt *et al.* (2004) |
| Diclofenac | | Kindla *et al.* (2011) |
| Digoxin | | Kullak-Ublick *et al.* (2001) |
| Docetaxel | | Smith *et al.* (2005) |
| [D-penicillamine$^{2,5}$]enkephalin | | Kullak-Ublick *et al.* (2001) |
| Enalapril | | Liu *et al.* (2006) |
| Epicatechin gallate | 34 | Roth *et al.* (2011b) |
| Epigallocatechin gallate | 13 | Roth *et al.* (2011b) |
| Erythromycin | | Franke *et al.* (2008) |
| Estradiol-17β-glucuronide | 5–25 | Konig *et al.* (2000a); Cui *et al.* (2001); Hirano *et al.* (2004) |
| Estrone-3-sulphate | | Kullak-Ublick *et al.* (2001); Nozawa *et al.* (2004b); Nozawa *et al.* (2005) |
| Fexofenadine | 108 | Shimizu *et al.* (2005) |
| Fluorescein | | Gui *et al.* (2010) |
| Fluorescein methotrexate | 7.9 | Gui *et al.* (2010) |
| Fluo-3, pentoammonium salt | 6.8 | Baldes *et al.* (2006) |
| Flutax-2 | | Gui *et al.* (2010) |
| Fluvastatin | 7 | Kopplow *et al.* (2005) |
| Glutathione | 4500 | Briz *et al.* (2006) |
| Glycocholate | 43 | Kullak-Ublick *et al.* (2001); Briz *et al.* (2006) |
| Glycoursodeoxycholate | 24.7 | Maeda *et al.* (2006b) |
| Hydroxyurea | | Walker *et al.* (2011) |

## Table 2

*Continued*

| Substrates | $K_m$ (μM) | References |
|---|---|---|
| Imatinib | | Hu *et al.* (2008) |
| Leukotriene C4 | | Konig *et al.* (2000a); Kullak-Ublick *et al.* (2001) |
| Mesalazine | 77 | Konig (2011) |
| Methotrexate | 25–39 | Abe *et al.* (2001) |
| Microcystin | 1.2–9 | Fischer *et al.* (2005); Komatsu *et al.* (2007) |
| Monoglyucuronosyl bilirubin | 0.5 | Cui *et al.* (2001) |
| Mycophenolic acid-7-O-glucuronide | 114 | Picard *et al.* (2010) |
| Nafcillin | 73 | Nakakariya *et al.* (2008) |
| Olmesartan | 44–72 | Nakagomi-Hagihara *et al.* (2006); Yamada *et al.* (2007) |
| Ouabain | | Kullak-Ublick *et al.* (2001) |
| Paclitaxel | 7 | Smith *et al.* (2005) |
| Phalloidin | 8 | Meier-Abt *et al.* (2004) |
| Pitavastatin | 3–4 | Hirano *et al.* (2004); Fujino *et al.* (2005) |
| Rifampicin | 2 | Vavricka *et al.* (2002); Tirona *et al.* (2003) |
| Ro 48–5033 | 166 | Treiber *et al.* (2007) |
| Rosuvastatin | 10 | Ho *et al.* (2007) |
| S-8921G | 1.88 | Sakamoto *et al.* (2008) |
| Saquinavir | | Hartkoorn *et al.* (2010) |
| Taurocholate | 6–112 | Abe *et al.* (2001); Kullak-Ublick *et al.* (2001); Letschert *et al.* (2004); Briz *et al.* (2006) |
| Taurochenodeoxycholate | | Briz *et al.* (2006) |
| Taurodeoxycholate | | Briz *et al.* (2006) |
| Tauroursodeoxycholate | 16 | Maeda *et al.* (2006b) |
| Telmisartan | 1 | Ishiguro *et al.* (2006) |
| Thyroxine (T4) | | Kullak-Ublick *et al.* (2001) |
| TR-14035 | 5.3 | Tsuda-Tsukimoto *et al.* (2006) |
| Triiodothyronine (T3) | 6 | Abe *et al.* (2001); Kullak-Ublick *et al.* (2001) |
| Valsartan | 18 | Yamashiro *et al.* (2006) |
| OATP1C1 | | |
| Bromosulphophthalein | | Pizzagalli *et al.* (2002) |
| Estradiol-17β-glucuronide | | Pizzagalli *et al.* (2002) |
| Estrone-3-sulphate | | Pizzagalli *et al.* (2002) |
| Thyroxine (T4) | 0.09 | Pizzagalli *et al.* (2002) |
| Triiodothyronine (T3) | | Pizzagalli *et al.* (2002) |
| Reverse triiodothyronine (rT3) | 0.128 | Pizzagalli *et al.* (2002) |
| Thyroxine sulphate (T4S) | | van der Deure *et al.* (2008) |

If available, apparent affinity ($K_m$) values are listed. This table is an updated and extended version of a similar table published in Hagenbuch and Gui (2008).

ACU154: metabolite of PKI166, an epidermal growth factor receptor kinase inhibitor; Bamet-R2: *cis*-diammine-chloro-cholylglycinate-platinum(II); Bamet-UD2: *cis*-diammine-bisursodeoxycholate-platinum(II); BDE47: 2,2′,4,4′-Tetrabromodiphenyl ether; BDE99: 2,2′,4,4′,5-pentabromodiphenyl ether; BDE153: 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BQ-123: cyclic pentapeptide endothelin receptor antagonist; CDCA-NBD: chenodeoxycholyl-(Nε-NBD)-lysine; CRC220: peptidomimetic thrombin inhibitor; Flutax-2: paclitaxel, Oregon Green® 488 conjugate; Gd-B20790: gadolonium-18-((3-(2-carboxylbutyl)-2,4,6-triiodophenyl)amino)-3,6,9-tris(carboxymethyl)-11,18-dioxo-3,6,9,12-tetrazaoctadecanoic acid; Ro 48–5033: Bosentan metabolite; SN-38: 7-ethyl-10-hydroxycamptothecin (active metabolite of irinotecan); S-8921G: methyl 1-(3,4-dimethoxyphenyl)-(3-ethylvaleryl)-4-hydroxy-6,7,8-trimethoxy-2-naphthoate glucuronide (inhibitor of the ilial apical sodium-dependent bile acid transporter); TR-14035: α4β1/α4β7 integrin dual antagonist.

## Table 3

Substrates of human OATP2 family

| Substrates | $K_m$ (μM) | References |
|---|---|---|
| OATP2A1 | | |
| Latanoprost acid | 5.4 | Kraft *et al.* (2010) |
| $PGH_2$ | 0.4 | Chi and Schuster (2010) |
| $PGE_1$ | 0.07 | Kanai *et al.* (1995) |
| $PGE_2$ | 0.09 | Kanai *et al.* (1995) |
| $PGF_{2\alpha}$ | 0.1 | Kanai *et al.* (1995) |
| Thromboxane $B_2$ | 0.4 | Kanai *et al.* (1995) |
| OATP2B1 | | |
| Aliskiren | 72 | Vaidyanathan *et al.* (2008) |
| Atorvastatin | 0.2 | Grube *et al.* (2006b) |
| Benzylpenicillin | | Tamai *et al.* (2000) |
| BDE47 | 0.81 | Pacyniak *et al.* (2010) |
| BDE99 | 0.87 | Pacyniak *et al.* (2010) |
| BDE153 | 0.65 | Pacyniak *et al.* (2010) |
| Bosentan | 202 | Treiber *et al.* (2007) |
| Bromosulphophthalein | 0.7 | Kullak-Ublick *et al.* (2001) |
| CP-671,305 | 4 | Kalgutkar *et al.* (2007) |
| Dehydroepiandrosterone-3-sulphate | 9 | Pizzagalli *et al.* (2003) |
| Eltrombopag | | Takeuchi *et al.* (2011) |
| Estrone-3-sulphate | 5–21 | Tamai *et al.* (2001); Pizzagalli *et al.* (2003); Nozawa *et al.* (2004a); Hirano *et al.* (2006); Grube *et al.* (2006a) |
| Ezetimibe glucuronide | | Oswald *et al.* (2008) |
| Fexofenadine | | Nozawa *et al.* (2004a) |
| Fluvastatin | 0.7 | Kopplow *et al.* (2005); Noe *et al.* (2007) |
| Glibenclamide | 6 | Satoh *et al.* (2005) |
| Latanoprost acid | | Kraft *et al.* (2010) |
| M17055 | 4.5 | Nishimura *et al.* (2007) |
| Mesalazine | 189 | Konig (2011) |
| Montelukast | | Mougey *et al.* (2009) |
| Pravastatin | 2 | Nozawa *et al.* (2004a) |
| Pitavastatin | 1.2 | Hirano *et al.* (2006) |
| Pregnenolone sulphate | | Grube *et al.* (2006a) |
| $PGE_2$ | | Tamai *et al.* (2000) |
| Rosuvastatin | 2 | Ho *et al.* (2006) |
| Talinolol | 629 | Shirasaka *et al.* (2010) |
| Taurocholate | 72 | Kobayashi *et al.* (2003) |
| Tebipenem pivoxil | | Kato *et al.* (2010) |
| Thyroxine (T4) | 0.77 | Leuthold *et al.* (2009) |
| Unoprostone metabolite | 91 | Gao *et al.* (2005) |

If available, apparent affinity ($K_m$) values are listed. This table is an updated and extended version of a similar table published in Hagenbuch and Gui (2008).
BDE47: 2,2′,4,4′-Tetrabromodiphenyl ether; BDE99: 2,2′,4,4′,5-pentabromodiphenyl ether; BDE153: 2,2′,4,4′,5,5′-hexabromodiphenyl ether; CP-671,305: (+)-2-[4-((2-(benzol[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-3-fluoro-phenoxy]-propionic acid; M17055: 7-chloro-2,3-dihydro-1-(2-methylbenzoyl)-4(1*H*)-quinolinone 4-oxime-O-sulphonic acid.

## Table 4

Substrates of human OATP families 3–6

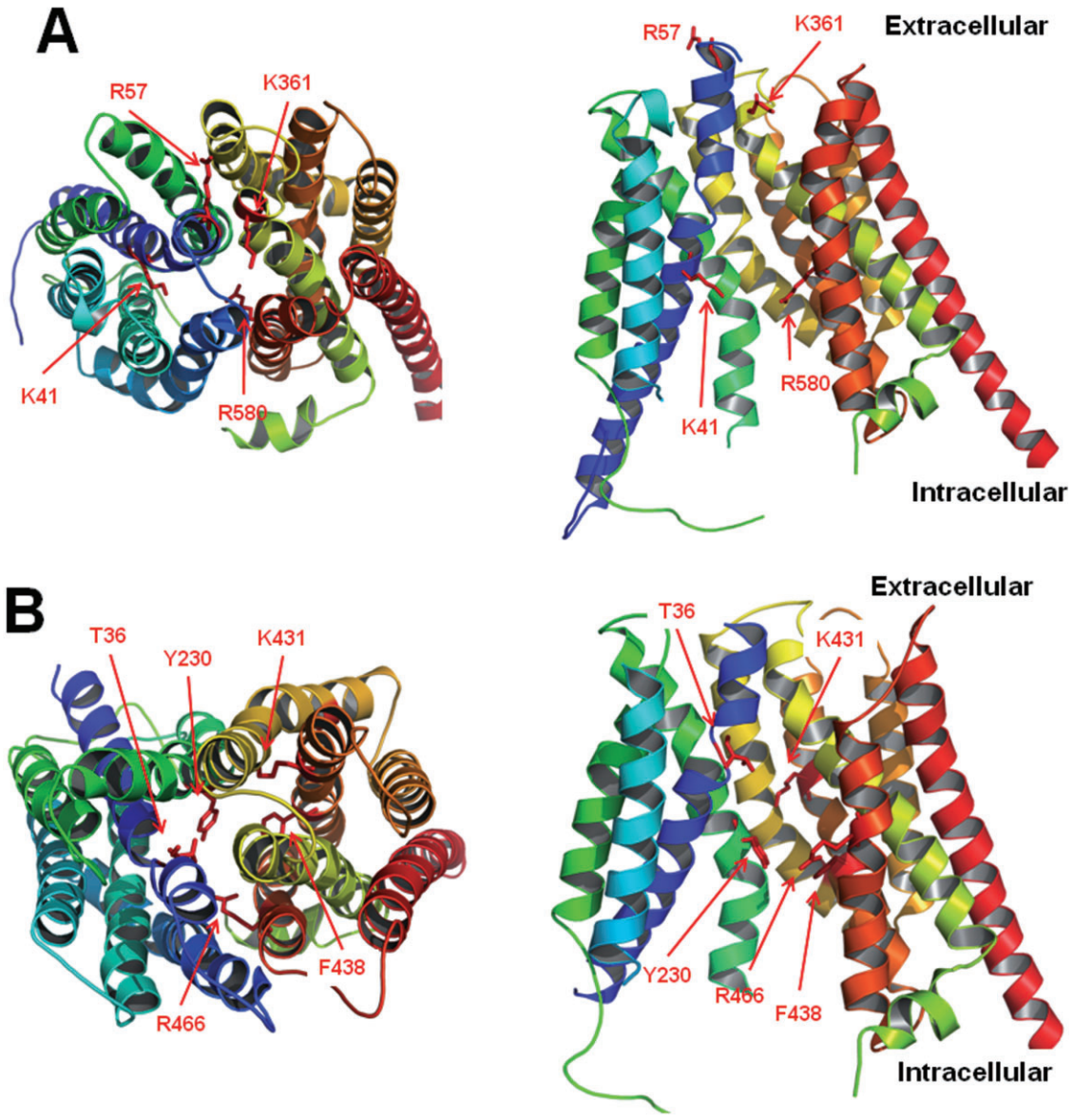
| Substrates | $K_m$ (μM) | References |
|---|---|---|
| OATP3A1_v1 | | |
| Benzylpenicillin | | Tamai *et al.* (2000) |
| BQ-123 | | Huber *et al.* (2007) |
| Deltorphin | | Huber *et al.* (2007) |
| Estrone-3-sulphate | | Tamai *et al.* (2000) |
| $PGE_1$ | 0.05–0.1 | Adachi *et al.* (2003); Huber *et al.* (2007) |
| $PGE_2$ | 0.06–0.2 | Tamai *et al.* (2000); Adachi *et al.* (2003); Huber *et al.* (2007) |
| $PGF_{2\alpha}$ | | Adachi *et al.* (2003) |
| Thyroxine (T4) | | Huber *et al.* (2007) |
| Vasopressin | | Huber *et al.* (2007) |
| OATP3A1_v2 | | |
| Arachidonic acid | | Huber *et al.* (2007) |
| BQ-123 | | Huber *et al.* (2007) |
| $PGE_1$ | 0.2 | Huber *et al.* (2007) |
| $PGE_2$ | 0.4 | Huber *et al.* (2007) |
| Thyroxine (T4) | | Huber *et al.* (2007) |
| Vasopressin | | Huber *et al.* (2007) |
| OATP4A1 | | |
| Benzylpenicillin | | Tamai *et al.* (2000) |
| Estradiol-17β-glucuronide | | Tamai *et al.* (2000) |
| Estrone-3-sulphate | | Tamai *et al.* (2000) |
| Thyroxine (T4) | | Fujiwara *et al.* (2001) |
| $PGE_2$ | | Tamai *et al.* (2000) |
| Triiodothyronine (T3) | 1 | Fujiwara *et al.* (2001) |
| Reverse triiodothyronine (rT3) | | Fujiwara *et al.* (2001) |
| Taurocholate | 15 | Fujiwara *et al.* (2001) |
| Unoprostone metabolite | | Gao *et al.* (2005) |
| OATP4C1 | | |
| cAMP | | Mikkaichi *et al.* (2004) |
| Digoxin | 8 | Mikkaichi *et al.* (2004) |
| Estrone-3-sulphate | 27 | Yamaguchi *et al.* (2010) |
| Methotrexate | | Mikkaichi *et al.* (2004) |
| Ouabain | 0.4 | Mikkaichi *et al.* (2004) |
| Sitagliptin | | Chu *et al.* (2007) |
| Thyroxine (T4) | | Mikkaichi *et al.* (2004) |
| Triiodothyronine (T3) | 6 | Mikkaichi *et al.* (2004) |

If available, apparent affinity ($K_m$) values are listed.
BQ-123: cyclic pentapeptide endothelin receptor antagonist.

However, to identify the individual amino acids that are involved in substrate translocation, additional experiments such as cysteine scanning mutagenesis and eventually crystallography or NMR studies are needed. Because there is evidence that different substrates are handled slightly differently by at least OATP1B1 and OATP1B3 (Gui *et al.*, 2008; Roth *et al.*, 2011a,b), such experiments will have to be performed for multiple model substrates.

## *Pathology and clinical significance*

There are only a few links between disease states and altered function of OATPs; however, there have been many studies showing associations between altered OATP expression levels and disease states, and documenting effects of different alleles and single-nucleotide polymorphisms (SNPs) in OATPs on drug disposition.




## Figure 2

Homology models of members of the *SLCO* (OATP1B1) and the *SCL22A* (OAT1) families. The models were generated using Phyre[2] (Kelley and Sternberg, 2009) and are based on the *E. coli* glycerol-3-phosphate transporter. (A) OATP1B1 is shown viewed from the extracellular side (left) and from within the lipid bilayer (right). For clarity, transmembrane domains 2 and 4 are omitted in the right panel. Amino acids mentioned in the text are indicated. (B) OAT1 is shown viewed from the extracellular side (left) and from within the lipid bilayer (right). For clarity, transmembrane domains 2 and 4 are omitted in the right panel. The indicated amino acids were identified as important for the function of OAT1 and face the putative aqueous pore (Hong *et al.*, 2004; Perry *et al.*, 2006; Rizwan *et al.*, 2007).

Neonates with the OATP1B1 polymorphism N130D (found in OATP1B1*1b and *15) are at a higher risk for developing severe hyperbilirubinaemia (Huang *et al.*, 2004; Buyukkale *et al.*, 2011). Adults with the OATP1b1*15 haplotypes also have higher serum bilirubin levels (Ieiri *et al.*, 2004), though there is no associated pathology. However, OATP expression is often altered in disease states. Cholestasis results in decreased mRNA levels of OATP1A2, OATP1B1 and OATP1B3 in whole livers (Keitel *et al.*, 2005; Chen *et al.*, 2008; Congiu *et al.*, 2009). Placental expression of OATP1A2 mRNA is increased in patients with intrahepatic cholestatis of pregnancy (Cui *et al.*, 2009). OATP1B1 is also reduced in patients with severe versus mild viral hepatitis (Oswald *et al.*, 2001). Inflammatory bowel disease is associated with higher OATP2B1 and OATP4A1 levels in ileum and colon (Wojtal *et al.*, 2009), and OATP4A1 is also up-regulated in polycystic ovarian syndrome (Plaza *et al.*, 2010).

Of particular interest are several SNPs in OATP1B1, which have demonstrated the importance of this transporter in the disposition of certain drugs. The N130D allele, found in both OATP1B1*1b and *15, is associated with altered pharmacokinetics of pravastatin and pitavastatin (Nishizato *et al.*, 2003;

Mwinyi *et al.*, 2004; Niemi *et al.*, 2004; Chung *et al.*, 2005; Wen and Xiong, 2010). The V174A allele, which is found in both OATP1B1*5 and OATP1B1*15, is associated with an attenuated cholesterol lowering effect of multiple statins (Tachibana-Iimori *et al.*, 2004) as well as with an increased systemic exposure of the anti-diabetic nateglinide (Zhang *et al.*, 2006) and the HIV protease inhibitor lopinavir (Hartkoorn *et al.*, 2010). However, the V174 allele is unrelated to the pharmacokinetics of rosiglitazone and pioglitazone (Kalliokoski *et al.*, 2008), torasemide (Werner *et al.*, 2008), mycophenolic acid (Miura *et al.*, 2007) or telmisartan (Miura *et al.*, 2009). Polymorphisms in other OATPs, while less studied, can also affect drug pharmacokinetics. It has recently been shown that OATP1A2 polymorphisms are associated with imatinib clearance (Yamakawa *et al.*, 2011), and polymorphisms in OATP2B1 are associated with the pharmacokinetics of fexofenadine (Akamine *et al.*, 2010). Functional OATP polymorphisms are reviewed in detail by Kalliokoski and Niemi (2009) and Konig (2011).

Many cancer tissues and cell lines have altered expression of OATPs. For example, the normally liver-exclusive OATP1B3 is also expressed in gastric, colon and pancreatic cancers (Abe *et al.*, 2001; Lee *et al.*, 2008), as well as cancers of the lung (Monks *et al.*, 2007), breast (Muto *et al.*, 2007) and prostate (Hamada *et al.*, 2008), whereas it has a reduced expression in hepatocellular carcinomas (Kinoshita and Miyata, 2002; Cui *et al.*, 2003; Vavricka *et al.*, 2004). Similarly, most of the other OATPs have been shown to have altered expression in different types of cancers. Because OATPs are known to transport hormones and their conjugates, which are thought to play a role in the enhanced proliferation or chemo-resistance of some cancers, the overexpression of OATPs may provide a survival benefit to these cells. The role of OATPs in cancer is discussed further in the reviews by Obaidat *et al.* (2012) and Wlcek *et al.* (2011).

One of the primary pathologies caused by OATPs is likely to be adverse drug–drug or drug–food interactions. Treatment with cyclosporine, an inhibitor of OATP-mediated transport, is associated with increased plasma concentrations of statins (Neuvonen *et al.*, 2006). Cyclosporine also increases the plasma concentration of bosentan, as does rifampicin, both of which inhibit OATP-mediated bosentan uptake at clinically relevant concentrations (Treiber *et al.*, 2007; van Giersbergen *et al.*, 2007). Both rifamycin SV and rifampicin reduce bromosulphophthalein (BSP) elimination in humans and inhibit *in vitro* uptake of BSP by OATP1A2, OATP1B1, OATP1B3 and OATP2B1 (Vavricka *et al.*, 2002). Macrolide antibiotics also inhibit uptake of BSP and pravastatin by OATP1B1 and OATP1B3 *in vitro* (Seithel *et al.*, 2007). In addition, cyclosporine, saquinavir, indinavir and rifamycin SV inhibit uptake of estradiol-17β-glucuronide by OATP1B1 with potencies that correlate with the incidence of hyperbilirubinaemia associated with those four drugs (Campbell *et al.*, 2004).

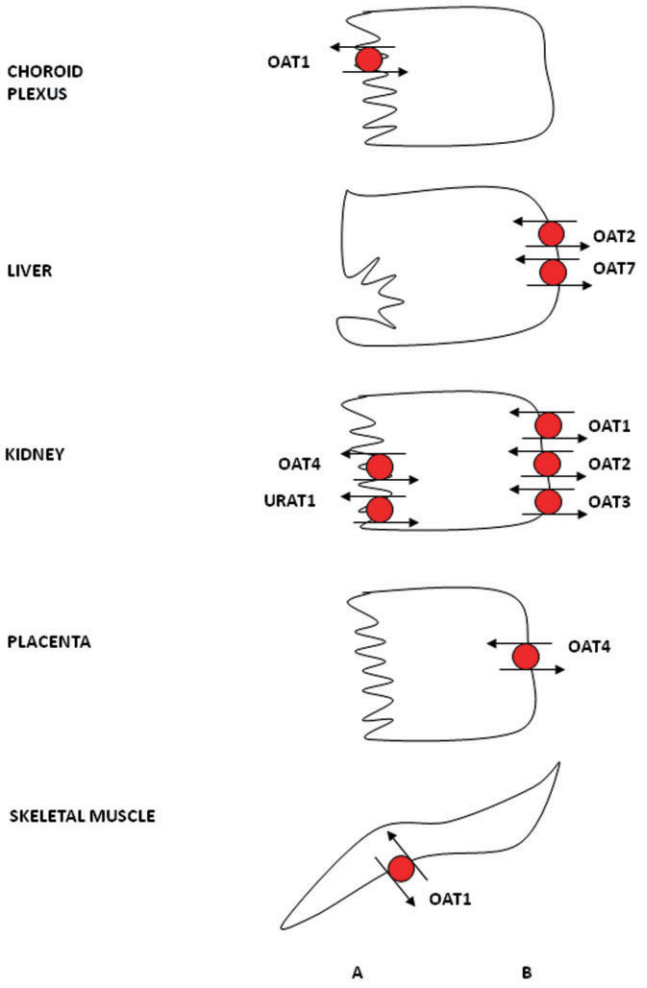
There are also reports on potential drug–food interactions occurring at OATPs, particularly for OATP1A2 and OATP2B1, which are expressed at the luminal membrane of enterocytes. Fruit juices decrease the oral bioavailability of fexofenadine in humans (Dresser *et al.*, 2002; 2005; Glaeser *et al.*, 2007). It has been shown that fexofenadine is a substrate of OATP1A2, and that uptake of fexofenadine by OATP1A2 is inhibited by naringin, a component of grapefruit (Bailey *et al.*, 2007). In addition, many flavonoids affect OATP-mediated uptake of the model substrates estrone-3-sulphate, estradiol-17β-glucuronide and dehydroepiandrosterone-3-sulphate (DHEAS), suggesting that possible drug–food interactions could occur especially in patients taking 'healthy' dietary supplements in addition to their prescribed medications (Wang *et al.*, 2005b; Roth *et al.*, 2011b).

## OATs

Organic anion transporters (OATs in humans, Oats in rodents) are another family of multispecific transporters and are encoded by the *SLC22/Slc22* gene superfamily. They mediate the transport of a diverse range of low molecular weight substrates including steroid hormone conjugates, biogenic amines, various drugs and toxins.

### *Tissue distribution*

Documented protein expression for OATs is summarized in Figure 3. Organic anion transporters are expressed in membranes of different tissues throughout the body. OAT1 was the first identified human OAT (Reid *et al.*, 1998), with mRNA expression at highest levels in the kidney, followed by skeletal muscle, brain and placenta (Hosoyamada *et al.*, 1999). At the protein level, OAT1 is expressed at the basolateral membrane of proximal tubules (Hosoyamada *et al.*, 1999; Motohashi *et al.*, 2002; Ljubojevic *et al.*, 2007) and in the plasma membrane of skeletal muscle cells (Takeda *et al.*, 2004). Membrane localization of human OAT1 in the choroid plexus has not yet been investigated, but Oat1 expression has been localized to the apical membrane of mouse and rat choroid plexus (Pritchard *et al.*, 1999; Alebouyeh *et al.*, 2003; Sykes *et al.*, 2004). OAT2 mRNA has the highest expression levels in the liver with lower levels also seen in kidney (Sekine *et al.*, 1998; Sun *et al.*, 2001; Hilgendorf *et al.*, 2007). Protein expression of OAT2 has been identified at the basolateral membrane of proximal tubules (Enomoto *et al.*, 2002b), and it is assumed to be expressed at the basolateral membrane of human hepatocytes based on findings in rodents. OAT3 mRNA has highest expression levels in the kidney with lower levels in brain (Cha *et al.*, 2001; Hilgendorf *et al.*, 2007). OAT3 mRNA expression has also been shown in adrenal tissue and the human adrenal cell line NCI-H295R, and functional studies suggest the protein is expressed (Asif *et al.*, 2005). OAT3 protein has been localized to the basolateral membrane of proximal tubules in the kidney (Cha *et al.*, 2001). OAT4 mRNA is expressed in kidney and placenta (Cha *et al.*, 2000; Bleasby *et al.*, 2006), with protein identified at the apical membrane of renal proximal tubules (Babu *et al.*, 2002; Ekaratanawong *et al.*, 2004) and at the basolateral membrane of syncytiotrophoblasts in the placenta (Ugele *et al.*, 2003). Similarly to OAT3, OAT4 mRNA expression and function has also been shown in adrenal tissue and the human adrenal cell line NCI-H295R (Asif *et al.*, 2005). Little is known about human OAT5, although Northern blot analysis demonstrates mRNA expression in the liver (Sun *et al.*, 2001). The recently characterized OAT7 has been shown to be exclusively expressed in adult and fetal liver, where its expression has been localized to the basolateral membrane of hepatocytes



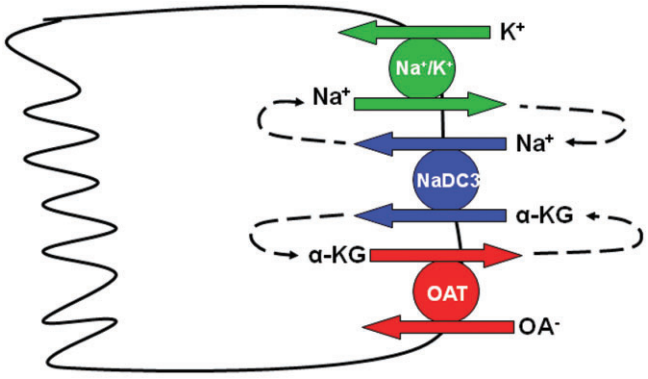

## Figure 3

Expression of OATs in different human epithelia. For more details, see the text. OAT1 localization in the choroid plexus and OAT2 localization in the liver is inferred from rodent data. (A) apical; (B) basolateral.

(Shin *et al.*, 2007). OAT10 mRNA has been shown to have highest expression levels in the kidney followed by brain, heart, small intestine and colon (Nishiwaki *et al.*, 1998; Bahn *et al.*, 2008). URAT1, which was previously named the renal-specific transporter 'RST', has mRNA expression in both adult and fetal kidney (Enomoto *et al.*, 2002a); more recently, mRNA was also identified in vascular smooth muscle cells (Price *et al.*, 2006). Using immunohistochemistry, URAT1 protein has been localized to the apical membrane of renal proximal tubules (Enomoto *et al.*, 2002a).

## *Substrate specificity*

The first cloning of human OAT1 was reported in 1998 (Reid *et al.*, 1998). Additional reports in 1999 described the initial functional characterization of human OAT1 as a multispecific organic anion-dicarboxylate exchanger (Cihlar *et al.*, 1999; Hosoyamada *et al.*, 1999; Lu *et al.*, 1999; Race *et al.*, 1999). The best characterized OATs, OAT1 and OAT3, have been




## Figure 4

Cartoon of tertiary active transport mechanism for OAT-mediated uptake of organic anions. The primary active $Na^+/K^+$-ATPase generates the sodium gradient that is used by the secondary active $Na^+$-dicarboxylate cotransporter (NaDC3) to maintain a high intracellular concentration of α-ketoglutarate, which is used to drive uptake of other organic anions by OAT1 and OAT3.

shown to transport organic anions against a negative membrane potential in exchange for the counter ion α-ketoglutarate. The α-ketoglutarate gradient is maintained by the secondary active sodium-dicarboxylate co-transporter, which utilizes the sodium gradient maintained by the primary active $Na^+/K^+$ ATPase (see Figure 4). Therefore, transport of these OATs has been termed 'tertiary active.' Unlike OAT1 and OAT3, human OAT7 exhibits a unique exchange mechanism using short chain fatty acids such as butyrate as counter ions for the transport of sulphate conjugates (Shin *et al.*, 2007). OAT1 is primarily known for its high affinity transport of p-aminohippurate (PAH) from renal tubule cells with apparent affinity ($K_m$) values reported in the low micromolar range (Hosoyamada *et al.*, 1999). OAT3 can also transport PAH but with slightly lower affinity than OAT1 (Cha *et al.*, 2001). Aside from PAH, OAT1 has been shown to transport prostaglandins, α-ketoglutarate, NSAIDs, antivirals and anticancer drugs. The uricosuric drug, probenecid, is a potent inhibitor of OAT1 transport (Sweet *et al.*, 1997; Cihlar *et al.*, 1999; Hosoyamada *et al.*, 1999; Lu *et al.*, 1999; Race *et al.*, 1999). A more comprehensive review of all OAT substrates and inhibitors can be found in tables of recently published reviews by VanWert *et al.* (2010) and Burckhardt and Burckhardt (2011).

## *Regulation of expression*

Transcriptional regulation of OATs has been studied by several groups and multiple transcription factors have been implicated. HNF-1α and/or HNF-1β have been shown to affect expression of human OAT1 (Saji *et al.*, 2008), OAT3 (Kikuchi *et al.*, 2006) and URAT1 (Kikuchi *et al.*, 2007), while HNF-4α seems to be involved in human OAT2 expression (Popowski *et al.*, 2005). In addition, for both OAT3 (Kikuchi *et al.*, 2006) and URAT1 (Kikuchi *et al.*, 2007), epigenetic mechanisms of regulation have been identified. At the protein level, PKC activation results in internalization and thus functional inhibition of human OAT1 in frog oocytes,

HEK293 cells and Cos-7 cells (Wolff *et al.*, 2003; Zhang *et al.*, 2008). Activation of PKA resulted in stimulation of PAH uptake into opossum kidney cells, indicating that OAT1 could be stimulated by agents that activate PKA (Sauvant *et al.*, 2001; 2002); however, these effects seem to depend on the agents used to stimulate the kinase (Sauvant *et al.*, 2006). Additional studies are needed to investigate what consequences and effects drugs that inhibit or stimulate activation of protein kinases have on human OATs (VanWert *et al.*, 2010).

### *Transporter structure*

The size of OATs ranges from 542 amino acids for human OAT3 to 563 amino acids for OAT1. Like OATPs, OATs are predicted to have 12 transmembrane domains with intracellular amino and carboxy-termini. There is a large extracellular loop between transmembrane domains 1 and 2, as well as a large intracellular loop between transmembrane domains 6 and 7. The large extracellular loop contains potential N-glycosylation sites, while the large intracellular loop and the carboxy-terminus contain putative phosphorylation sites. The extra- and intracellular locations of the different loops were experimentally supported for human OAT1 (Hong *et al.*, 2007).

As is the case for the OATPs, there is so far no crystal structure available for any of the OATs. Therefore, homology modelling has been used to predict the putative three-dimensional structure of human OAT1 on the basis of the bacterial glycerol-3-phosphate transporter and the lactose permease (Perry *et al.*, 2006). Several groups have used site-directed mutagenesis coupled with functional experiments to investigate the role of individual amino acids identified, for example, from polymorphism studies (Bleasby *et al.*, 2005; Fujita *et al.*, 2005; Erdman *et al.*, 2006; Zhou *et al.*, 2010). Some of these amino acids are highlighted in the predicted three-dimensional structure of OAT1 shown in Figure 2B. For more details, please see Burckhardt and Burckhardt (2011).

More recently, a molecular dynamics simulation was performed for OAT1 based on the homology model developed. The data indicate that during the 100 ns simulation one pair of transmembrane domains in each half of the transporter tilt, suggesting a possible involvement in the opening and closing of the transporter (Tsigelny *et al.*, 2011). However, such molecular simulation based on a homology model will most likely improve once a crystal structure is available.

### *Pathology and clinical significance*

Knockout mice for Oat1 (Eraly *et al.*, 2006) and Oat3 (Sweet *et al.*, 2002) have been generated and are both viable and fertile. Characterization of Oat1 null mice showed decreased *in vivo* transport of Oat1 substrates such as PAH and furosemide, but not of estrone-3-sulphate, a substrate of Oat3 (Eraly *et al.*, 2006). Renal slices from Oat3 null mice demonstrated decreased transport of estrone-3-sulphate, taurocholate and PAH (Sweet *et al.*, 2002). These animal models are important tools to investigate whether Oat1 or Oat3 is primarily responsible for the transport of common drug substrates, but potential species differences must be considered when extrapolating to the human situation (Nigam *et al.*, 2007).

For both OAT1 and OAT3, a lower than average mutation rate has been described (Urban *et al.*, 2006). Although several non-synonymous polymorphisms exist for both transporters, only a few have been shown to affect the transport function (Srimaroeng *et al.*, 2008). The only member of the OAT family for which mutations have been linked to a disease is URAT1. The first characterized mutation that was shown to result in familial idiopathic hypouricaemia is a missense mutation leading to a premature stop codon (W258X). It was first reported by Enomoto *et al.* (2002a), and later additional mutations have been described in patients with hypouricaemia (Anzai *et al.*, 2007).

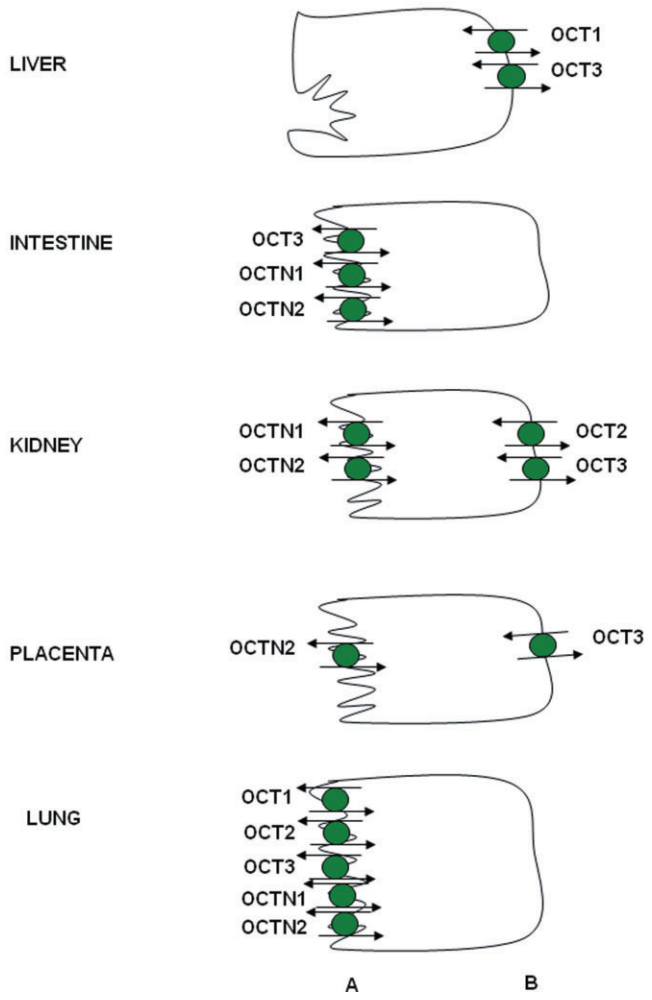
Because of the broad substrate specificity of OATs, drug–drug interactions are possible especially with drugs that are eliminated by OAT1 or OAT3 in the kidneys. The interaction between probenecid and methotrexate that was first described in 1978 (Aherne *et al.*, 1978a,b) can today be explained by probenecid's inhibition of OAT3- and OAT1-mediated methotrexate transport (Nozaki *et al.*, 2007). Similarly, co-administration of probenecid with furosemide and other loop diuretics can decrease the potency of these diuretics by reducing their OAT-mediated secretion in the proximal tubule (Burckhardt and Burckhardt, 2011). However, such drug–drug interactions are not always detrimental: for instance, co-administration with probenecid is used to decrease the OAT1- and OAT3-mediated renal elimination of penicillin and other β-lactam antibiotics (Burckhardt and Burckhardt, 2011).

## OCTs

In addition to the OATs described above, the *SLC22A* family also contains the organic cation transporters (OCT1, OCT2 and OCT3) and the organic cation and carnitine transporters (OCT6, OCTN1 and OCTN2). Like the OATPs and OATs, OCTs are multispecific uptake transporters expressed in numerous epithelia throughout the body.

### *Tissue distribution*

Protein expression of OCTs is summarized in Figure 5. OCT1 is usually considered to be a liver-specific transporter, along with OATP1B1 and OATP1B3. However, weak expression of OCT1 mRNA has been seen in other tissues, such as heart, skeletal muscle, kidney, brain and placenta (Gorboulev *et al.*, 1997; Zhang *et al.*, 1997). In the liver, OCT1 protein is localized to the basolateral membrane of hepatocytes (Nies *et al.*, 2008). Furthermore, OCT1 protein was localized to the luminal membrane of lung epithelial cells (Lips *et al.*, 2005). Although rodent Oct1 protein has been identified at the basolateral membrane of enterocytes and proximal tubule epithelial cells (Karbach *et al.*, 2000), *in situ* hybridization did not detect OCT1 expression in human kidney (Gorboulev *et al.*, 1997). OCT2 is generally considered to be a kidney transporter, though mRNA is expressed at low levels in other tissues such as spleen, placenta, small intestine and brain (Gorboulev *et al.*, 1997). OCT2 protein is mainly localized to the luminal membrane of the distal convoluted tubules (Gorboulev *et al.*, 1997). OCT2 has also been identified in the pyramidal cells of the cerebral cortex and hippocampus




## Figure 5

Expression of OCTs in human epithelial cells. For more details, see the text. Localization of OCTN1 in the kidney is concluded based on rodent data. (A) apical; (B) basolateral.

(Busch *et al.*, 1998) as well as the luminal membrane of lung epithelia (Lips *et al.*, 2005). OCT3, also known as the extraneuronal monoamine transporter (EMT), has the widest tissue distribution of the OCTs, with strong mRNA expression in liver, placenta, kidney and skeletal muscle, and weaker signals in lung, heart and brain (Wu *et al.*, 2000). OCT3 protein expression has been confirmed on the basolateral membrane of hepatocytes (Nies *et al.*, 2009), the basal membranes of trophoblasts (Sata *et al.*, 2005), the apical membrane of enterocytes (Muller *et al.*, 2005) and the luminal membrane of lung epithelial cells (Lips *et al.*, 2005).

OCTN1, which was first cloned from a human fetal liver cDNA library, is expressed at the mRNA level in fetal liver, kidney and lung (Tamai *et al.*, 1997). In adults, mRNA is strongly expressed in kidney, trachea and bone marrow, and is weakly expressed in skeletal muscle, prostate, lung, pancreas, placenta, heart, uterus, spleen and spinal cord, as well as several cancer cell lines (Tamai *et al.*, 1997). OCTN2 mRNA expression is highest in heart, placenta, skeletal muscle, kidney and pancreas, though it is also expressed in brain, lung and liver (Wu *et al.*, 1998). Within the kidney, two different transcript sizes (3.5 and 4.0 kb) were detected for OCTN2 (Wu *et al.*, 1998). OCTN2 protein expression has been identified at the apical membrane of proximal tubules in kidney (Masuda *et al.*, 2006) and the apical membrane of syncytiotrophoblasts in placenta (Grube *et al.*, 2005). Both OCTN1 and OCTN2 are also expressed in bronchial epithelial cells, with the protein mainly localized to the apical membrane (Horvath *et al.*, 2007). OCT6 (CT2) was originally cloned from a human testis cDNA library and has been localized to Sertoli cells and epithelial cells of the epididymis (Enomoto *et al.*, 2002c). Expression of OCT6 mRNA is also seen in liver, hematopoietic cells and some cancer cell lines (Gong *et al.*, 2002).

### *Substrate specificity*

OCT1, OCT2 and OCT3 mediate the passive facilitated diffusion of a broad range of organic cations down their electrochemical gradients. As such, transport may occur in either direction, is independent of either sodium or pH, and transport of charged substrates is always electrogenic. Although OCT transporter action is independent of pH, affinity for certain substrates does depend on their degree of ionization, leading to increased transport of those substrates at reduced pH (Barendt *et al.*, 2002). Substrates include a wide variety of structurally unrelated small organic cations, both endogenous and exogenous, including many drugs. An extensive list of OCT1-3 substrates and inhibitors is included in a recent review on the importance of organic cation transporters in drug therapy (Nies *et al.*, 2011). Among these substrates are catecholamines, monoamine neurotransmitters and several antiviral drugs.

MPP (1-methyl-4-phenylpyridinium) is a commonly used model substrate for all three transporters; TEA (tetraethylammonium) is also commonly used for OCT1 and OCT2, although it is not a good substrate for OCT3 (Grundemann *et al.*, 1998). A pharmacophore model developed for OCT1 suggests that substrates contain a positive ionizable site, a hydrophobic site and two hydrogen bond acceptor sites (Moaddel *et al.*, 2007). A splice variant of OCT1 that lacks the carboxy-terminus of the protein was found to be nonfunctional for MPP transport (Hayer *et al.*, 1999). Alternatively, a somewhat longer splice variant of OCT2 that also contains a premature stop codon is found in human kidney, producing a protein which can still transport TEA, although it is less functional for MPP or cimetidine and cannot transport guanidine (Urakami *et al.*, 2002).

OCTN1, OCTN2 and OCT6 are all cation and carnitine transporters. OCTN1 transport activity can be affected by both sodium and proton gradients, depending on the substrate transported. OCTN2 also mediates both sodium-dependent and sodium-independent uptake, depending on the substrate (Koepsell *et al.*, 2007). In addition to carnitine, TEA is also a substrate of both transporters and is frequently used as a model substrate. OCTN2 appears to have different binding sites for TEA and L-carnitine, as several mutations have been found to inhibit carnitine but not TEA transport (Seth *et al.*, 1999). OCT6 has a much more limited substrate specificity than other organic cation transporters. Carnitine transport was found to be bidirectional and not fully depen-

dent on extracellular sodium, although transport was altered by both sodium and pH (Enomoto *et al.*, 2002c).

## *Regulation of expression*

OCT regulation appears to vary depending on transporter, species and tissue localization; therefore, it remains an area of active research. Regulation of OCTs can occur at the transcriptional or protein level. OCT1 has two response elements for HNF-4α, which interacts with them and activates transcription; this activation can be inhibited through SHP (Saborowski *et al.*, 2006). The OCT2 promoter region contains putative androgen receptor elements and steroid hormones increased both mRNA levels and activity of OCT2 in MDCK cells (Shu *et al.*, 2001). OCTN1 transcription was altered by both the RUNX1 transcription factor and TNF-α *in vitro* (Tokuhiro *et al.*, 2003).

OCT proteins contain phosphorylation sites for PKA, PKC, PKG and tyrosine kinase, and activation of these kinases can alter the activity of OCT1 and OCT2. OCT3 doesn't seem to be affected by PKA, PKC or PKG, despite several conserved target sequences; however, its activity is altered by both the MAP kinase pathway and the calcium–calmodulin pathway. PDZ family members interact with OCTN1 and OCTN2, and the interaction between PDZK1 and OCTN2 has been shown to stimulate transport (Kato *et al.*, 2005). The targeting of OCTN1 and OCTN2 to brush border membrane of enterocytes has also been shown to be regulated by PDZ domain proteins. Detailed summaries of the current knowledge of OCT regulation can be found in recent reviews by Ciarimboli and Schlatter (2005), Koepsell *et al.* (2007) and Ciarimboli (2008).

## *Transporter structure*

The organic cation transporting proteins contain between 543 and 557 amino acids. All are predicted to contain 12 transmembrane domains with intracellular amino and carboxy-termini. A large extracellular loop between the first and second transmembrane domains contains potential N-glycosylation sites, and a large intracellular loop between transmembrane domains 6 and 7 contains multiple putative phosphorylation sites. OCT1 and OCT2 have 70% amino acid identity to each other, and approximately 50% identity with OCT3 (Gorboulev *et al.*, 1997; Zhang *et al.*, 1997; Grundemann *et al.*, 1998). OCTN1 and OCTN2, which share 77% identity with each other, and 31–37% identity with OCT1-3, also contain an ATP/GTP binding motif in the second intracellular loop (Tamai *et al.*, 1997; Wu *et al.*, 1998). OCT6, also called CT2, has 36%, 38% and 37% identity to OAT1, OCT1 and OCTN2 respectively (Enomoto *et al.*, 2002c).

As has been done for the OATPs and OATs, homology modelling has been used to predict the putative three-dimensional structure of OCT1 (Popp *et al.*, 2005). According to this model, substrates seem to interact with OCT1 within a region rather than at a single binding site (Koepsell, 2011). Additional experiments demonstrated that five amino acids in the substrate binding region can interact with both extracellular and intracellular substrates and are thus likely part of the translocation pathway (Volk *et al.*, 2009; Koepsell, 2011). Furthermore, rat Oct1 has been expressed in a cell-free system, purified and reconstituted into proteoliposomes for functional characterization (Keller *et al.*, 2008). Production of OCT1 in such a cell-free system could be the first step towards the crystallization of this important drug transporter.

## *Pathology and clinical significance*

OCT1, OCT2 and OCT3 knockout mice have been generated and have no obvious phenotype (Jonker *et al.*, 2001; 2003; Zwart *et al.*, 2001). Similarly, no known polymorphisms in OCTs are associated with human pathologies. OCT1 has 18 SNPs that alter amino acids – six have reduced transport activity and one has increased activity (Kerb *et al.*, 2002). OCT2 has ten variants: with the exception of a premature stop codon, all are functionally active, though substrate selectivity and the ability to transport may be slightly altered (Koepsell *et al.*, 2007). Five non-synonymous polymorphisms have been identified in OCT3, three of which show reduced transport activity (Sakata *et al.*, 2010). As with the OATPs, it seems that the greatest risk of pathology associated with the organic cation transporters is that of adverse drug–drug interactions. OCT1 polymorphisms have been associated with altered pharmacokinetics of the antidiabetic metformin and the tyrosine kinase inhibitor imatinib, while a wide range of drugs have been implicated in potential drug–drug interactions as reviewed by Fahrmayr *et al.* (2010).

OCTN proteins, however, have been directly indicated in pathologies. Mutations in the gene cluster that contains the OCTN1 and OCTN2 genes have been associated with autoimmune diseases. OCTN1 variant L503F is associated with familial and sporadic inflammatory bowel disease (Lin *et al.*, 2010). Functionally, this variant has altered substrate specificity with a significantly increased affinity for the common model substrate TEA (Urban *et al.*, 2007). Systemic carnitine deficiency, which is caused by a lack of active reabsorption of carnitine in the kidney, has been associated with multiple mutations that cause low or impaired function of OCTN2 (Lahjouji *et al.*, 2001).

# Conclusion

Proteins encoded by the *SLCO* and *SLC22A* superfamilies are expressed in nearly every epithelium of the body, where they play a significant role in the absorption, distribution and elimination of drugs and other xenobiotics. Many members of these superfamilies transport a broad range of structurally diverse compounds, and several examples have been documented where transport proteins of the *SLCO* or *SLC22A* gene families were involved in adverse or intended drug–drug as well as drug–food interactions. Future studies should focus on the elucidation of the three-dimensional structure of these important drug uptake transporters because this will allow to predict and prevent such drug-related pathologies as well as to rationally design drugs targeted to individual tranpsorters. Overall, such studies will lead to a better and safer drug therapy.

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## Disclosure statement

The authors have nothing to disclose.

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